

## REMARKS

Claims 1-15, 32-34 and 36-47 are now pending. Claims 35 and 43 have been deleted without prejudice or disclaimer. Support for the amendment to claims 1 and 9 is found throughout the application, for instance, in the original claims and Example 1. Claims 6-7 and 37-40 have been amended to change the claim dependency. Claim 32 has been amended to correct the informal markings in the previously presented claim. Support for the amendment to claims 34 and 42 is found in unamended claim 34 and 42 and throughout the present application, for example, in paragraph [0035].

Applicants gratefully acknowledge the withdrawal of the prior rejections under 35 U.S.C. §§ 101, 102, 112, second paragraph, and nonstatutory obviousness-type double patenting.

### Indefiniteness

In response to the rejection under 35 U.S.C. §112, second paragraph, Applicants have amended claim 32 and submit herewith a clean set of amended claims as requested by the examiner. Thus, Applicants respectfully request withdrawal of this rejection.

### Nonstatutory Obviousness-Type Double Patenting

Applicants traverse the nonstatutory obviousness-type double patenting rejection of claims 1-15 and 32-47 over claims 16-17 and 19-25 of US Patent Application 10/675,225 in view of Stern. According to MPEP §804(II)(B)(1) “[w]hen considering whether the invention defined in a claim of an application would have been an obvious variation of the invention defined in the claim of a patent, the disclosure of the patent may not be used as prior art.” Based on the same reasoning, Applicants respectfully submit that the disclosure of secondary references may not be used to establish obviousness type double patenting. Thus, as page 7 of the Office action relies on the patent’s disclosure and Stern to establish obviousness type double patenting, the Applicants respectfully submit that an improper rejection was made. Moreover, the arguments below with respect to the traversal of the obviousness rejection may also apply here. Withdrawal of this rejection is respectfully requested.

### Enablement

Applicants traverse the rejection of claims 1-15 and 32-47 under 35 U.S.C. §112, first paragraph (enablement). Applicants’ counsel kindly requests a telephone conference with the examiner to clarify various points in the Office action as outlined below. Claims 34 and 42 have

been amended, which are directed to subject matter that is believed to be enabled according the Office action.

On page 3, item a), the Office states that to “identify a human patient that is susceptible” as “including normal healthy humans” because the claim “necessarily requires the absence of an ischemic event prior to the step of administering a nitroxide to a human patient.” Therefore, the Office appears to have read out of claims 1 and 34 the step of “identifying a human patient that is susceptible to ischemia.” Nonetheless, Applicants have amended claims 1 and 9 in part to state “the likelihood is reduced in comparison to a human patient who was not subject to the administering step.”

Also on page 3, item a), the Office states that “the term ‘identify a human patient that is susceptible’ reasonably encompasses various invasive and non-invasive medical procedures which may vary significantly in predictably *identifying humans with ischemia* (emphasis added) ....” It is not clear how “identifying humans with ischemia” is relevant to “identifying a human patient who is susceptible to ischemia” as recited in claims 1 and 34. Even if, for the sake of argument, one could not identify a patient, the methods at issue include an identifying step. Clarification of the Office’s statement is respectfully requested.

On page 4, item b) appears to be missing text after the word “and.” Clarification is respectfully requested so that the Applicants may address this point.

The Office states on page 4, item c) that

[a]lthough the instant specification provides support for a method of reducing the harmful effects of ischemia in human patient who is susceptible to ischemia by administering a sufficient amount of nitroxide to said patient prior to the onset ischemia, it does not reasonably provide enablement for preventing a harmful effect of ischemia in all tissues/organs in a human patient prior to the onset of ischemia ....

Claims 34 and 42 have been amended to include language that more closely resembles the language that the Office appears to suggest is enabled.

On page 4 of the Office action, item d), the Office states that “Stern discloses that in a clinical study as many as 90% of ischemic episodes were found to be silent ....” Clarification as to the relevance of this statement is respectfully requested.

The Office action states on page 8 that

the specification, while enabling for methods of reducing the harmful effects of ischemia comprising administering Tempol, does not reasonably provide enablement for preventing harmful effect of ischemia in a human patient prior to the onset of ischemia by administering all nitroxide compounds to said patient.

In view of the statement on page 4, item c) of the Office action as outlined above, Applicants respectfully request clarification of the subject matter that the Office believes supports an enabled claim. Nonetheless, based on a narrow interpretation of this statement, Applicants have amended claims 34 and 42 to recite tempol.

On page 11 of the action, under the heading “The relative skill of those the art,” the Office states that

it is doubtful that in the absence of evidence to show a correlation between ... preventing ischemia or harmful effects of ischemia ... and a common critical chemical feature of members of the genus of nitroxide compounds that an artisan would be able to reasonably practice the invention commensurate with the scope of the claims with respect to all nitroxide compounds without conducting extensive experimentation.

However, Applicants respectfully submit that nitroxides as recited in the application are generally a stable free radical compound (see [0024] of the present application). “Typically, ischemia ... results in the generation of free radicals which participate in killing cells.” (see [0021]). Thus, one of ordinary skill in the art would understand that generally “nitroxide [acts] as an antioxidant, or an ROS scavenger” (see [0021]). Thus, Applicants respectfully request clarification as to the evidence that is needed, if any, in addition to the above. Claims 1 and 9 have been amended to recite a “stable free radical” nitroxide.

The Office action states on page 12 that the terms in claims 9 and 16 “are not found to be supported by the instant disclosure.” However, claim 9 is an original claim and claim 16 has been canceled. Clarification of this statement is respectfully requested.

Page 13 of the Office action states that “showing enablement for single species does not render the entire nitroxide compound genus enabled.” However, according to the Training Materials for Examining Patent Applications with Respect to 35 U.S.C. Section 112, First Paragraph-Enablement of Chemical/Biotechnical Applications (Training Materials), “[f]or the claimed genus, representative examples together with the statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art - in view of the level of skill, state of the art and information in the specification - would expect the claimed genus could be used in that

matter without undue experimentation.” See Training Materials III, A, 1, c, iii. Applicants respectfully submit that the present specification had an example and statements applicable to the genus as a whole, which are discussed above. For example, a nitroxide is generally a stable free radical compound and typically, ischemia results in the generation of free radicals; the nitroxide may act as an anti-oxidant or an ROS scavenger. Applicants respectfully submit the requisite statement has been provided.

Moreover, Mitchell (US patent number 5,462,946), cited in the obviousness rejection, includes presumably enabled claims that recite methods for treating the effects of oxidative stress using some nitroxide compounds, which are also found in present claims 32-33 and those claims dependent thereon. Applicants respectfully submit that no more than routine experimentation would be required based on the knowledge of those having ordinary skill in the art. “The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation.” Please see MPEP § 2165. Therefore, Applicants respectfully submit that no more than routine experimentation is required. Withdrawal of the enablement rejection is respectfully requested.

Further, the Office action in the paragraph bridging pages 19-20 states that “it would have been within the skill and knowledge of an artisan skilled in the art to identify a patient susceptible of ischemia associated with medical procedures, including medical procedures for treating hemorrhage, aneurysm, as well as ischemia associated with endovascular procedures, without resorting to undue experimentation ....” Therefore, Applicants respectfully submit that claims 3-15, 33, 34, 36-40, 42, and 44-47 are believed to be enabled.

#### Obviousness

Applicants traverse the rejection of claims 1-15 and 32-47 under 35 U.S.C. §103 as obvious over Mitchell in view of Stern and Herfindal. The Office has not established a *prima facia* case of obviousness by establishing that predictable results would occur using the presently claimed methods or by establishing obviousness by any rationale in accordance with MPEP §2143.

For example, page 18, second paragraph of the Office action states: “[i]t would have been obvious ... to identify a person at risk of ischemia as taught by Stern prior to treating a patient with reperfusion injury ... by administering ... TEMPOL... as taught by Mitchell.” The Office has not established that a predictable result would occur by administering “*prior to the onset* of ischemia

(emphasis added)” as recited in independent claims 1-34 herein. Rather, Applicants respectfully submit that Mitchell recites “a method for treating the effects of oxidative stress due to the production of harmful oxygen-derived species .... [and] stress includes that due to oxidizing agents, increased oxygen exposure, oxygen-induced degeneration or disease, reperfusion injury, ionizing radiation, carcinogenic, chemotherapeutic, or mutagenic agents, aging, or arthritis.” Please see Mitchell, column 5, lines 26-35 and claim 12 (emphasis added).

In addition, the Office action states on page 19, lines 3-4 that Mitchell teaches tempol “for use as a protectant against oxidative stress in treating various conditions associated with oxidative stress such as reperfusion injury (e.g. MI) and strokes.” However, Applicants respectfully submit that Mitchell recites, in contrast, pharmaceutical compositions containing the nitroxide compounds for use as “[r]eperfusion injury protectants *effective in treating cardiovascular phenomenon such as ... strokes ...*” (column 3, lines 5-7, emphasis added). Again, Applicants respectfully submit that the Office has not established that predictable results would be obtained for the claimed methods that are directed in part to administering prior to onset of ischemia. Moreover, although Mitchell does not define “protectant,” it appears that, at least in some cases where this word is used, a protectant suggests protection from death after treating injury, rather than a protectant against the injury itself. See e.g., Mitchell, Figures 2 and 3, illustrating survival curves. Applicants respectfully submit that there is no motivation in Mitchell or any of the secondary references to arrive at the claimed invention that includes all of the steps recited in the claims herein.

Further, the Office states that Mitchell “provides a general teaching of ischemia and endovascular procedure;” however, Applicants are unclear where Mitchell provides such generalized teaching. Clarification kindly is requested. Nonetheless, even if for the sake of argument Mitchell disclosed a genus, MPEP §2144.08 states that the “ fact that a claimed species or subgenus is encompassed by a prior art genus is not sufficient by itself to establish a *prima facie* case of obviousness.” Applicants respectfully submit that the Office has not established *prima facie* obviousness for the rejected claims and specifically, for example, for ischemia arising from a medical procedures such as the treatment of hemorrhage, the treatment of an aneurysm, surgery, and endovascular procedure as recited in the relevant dependent claims.

With regard to claim 42, the Office action states on page 20 that “it is the examiner’s position that the sequence of ... first administering TEMPOL, then identifying a patient with

ischemia is within the skill ... in the art (see claim 42)." To clarify, Applicants respectfully submit that claim 42 includes in part the steps of "identifying a patient scheduled to undergo a medical procedure ... [and] administering to the patient, prior to the medical procedure ...."

In view of the foregoing comments, it is respectfully submitted that the present application is fully in condition for allowance and such action is earnestly solicited. If any questions remain, however, the Examiner is cordially invited to contact the undersigned attorney so that any such matters may be promptly resolved.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicant is not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicant reserves the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that Applicant has made any disclaimers or disavowals of any subject matter supported by the present application.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

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By: 

Carolyn A. Favorito  
Registration No. 39,183  
Attorney of Record  
Customer No. 20995  
(949) 760-0404